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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/681,284	10/09/2003	Ivan Ban	029300.52141US	2900

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CROWELL & MORING LLP
INTELLECTUAL PROPERTY GROUP
P.O. BOX 14300
WASHINGTON, DC 20044-4300

EXAMINER

UNDERDAHL, THANE E

ART UNIT	PAPER NUMBER
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1651

MAIL DATE	DELIVERY MODE
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12/13/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.		Applicant(s)	
	10/681,284		BAN ET AL.	
	Examiner		Art Unit	
	Thane Underdahl		1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,5,6 and 8-19 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5, 6 and 8-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- 1) ☒ Certified copies of the priority documents have been received.
- 2) ☐ Certified copies of the priority documents have been received in Application No. _____.
- 3) ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) ☒ Notice of References Cited (PTO-892) | 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) ☐ Notice of Informal Patent Application |
| 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) ☐ Other: _____ |

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DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/22/07 has been entered.

This Office Action is in response to the Applicant's request for continued examination received 8/22/07. Claims 1, 2, 5, 6 and 8-19 are pending. No claims are withdrawn. Claims 3, 4 and 7 are cancelled. Claim 1 has been amended. No claims are new.

Election of Species Remains in Effect

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The examiner wishes to remind the applicant that the election of species filed on 7/14/2006 remains in effect for examination of these amended claims. The elections were as follows:

Initial Aqueous Phase: an aqueous solution of a natural mixture of conjugated estrogens from pregnant mares' urine already depleted in phenolic constituents obtained by solid-phase or liquid-liquid extraction.

Non-conjugated Lipophilic Compound: non-conjugated flavonoids.

Extracting Agent: Ethyl Acetate.

Response to Applicant's Arguments— 35 U.S.C § 103

In the response submitted by the Applicant the 35 U.S.C § 102 (b) rejection of

claims 1, 2, 5, 6, 8-12 and 15-18 based on Turner et al. in view of Wang et al. as

supported by Klaassen et al., Merk Index and Neeb et al. is withdrawn in light of

applicant's amendment.

New Rejections

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Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 includes the statement "extracting agent which is at most only slightly miscible with water thereby extracting non-conjugated lipophilic compounds". This is a broad statement that does not exclude an extracting agent that also extracts conjugated lipophilic compounds which is the end result of the method. In the interest of compact prosecution, the Examiner will read the extracting agent that is suitable for extracting non-conjugated lipophilic compounds but not-suitable for conjugated lipophilic compounds.

The following is a quotation from 35 U.S.C. 112(a):

Claim 1 is rejected under 35 U.S.C. 103.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 2, 5, 6, 8-15-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Turner et al. (U.S. Patent # 2519516) in view of Wang et al. (WO 01/27134), Fritz et al. (U.S. Patent # 5071565) and Ban et al. (U.S. Patent # 5814624) in light of support

by Klaassen et al., Merk Index, Neeb et al., Hurst et al., Wikipedia ("Solvent") and "Dielectric Constant and Solubility".

These claims are drawn to a method to obtain a natural mixture of conjugated equine estrogens (**CEEs**) from pregnant mare urine (**PMU**). The method comprises the steps of subjecting an aqueous solution of a natural mixture of CEE already depleted in phenolic urine contents comprising phenol, cresol and dihydro-3,4-bis[(3-hydroxyphenyl)methyl]-2(3H)-furanone (**HPMF**) obtained by solid phase or liquid-liquid extraction. This solution that is depleted of said phenolic contents will be referred to as urine estrogen extract (**UEE**). The first step of the method is liquid-liquid extraction of UEE with an organic solvent extracting agent that is at most only slightly miscible with water thereby extracting non-conjugated lipophilic compounds (**NCLC**). The next step is the separation of the resulting aqueous phase. The organic extraction agent is ethyl acetate. The extraction with the organic solvent is can be repeated. The end result is an aqueous phase that is a natural mixture of CEEs that are depleted in NCLC such as non-conjugated flavonoids, non-conjugated isoflavanoids, and non-conjugated norisoprenoids.

Turner et al. teach a method to extract estrogen from PMU using a liquid-liquid extraction. Turner et al. teach an aqueous solution of conjugated estrogens (see Flow Sheet, Step F). The solution in Step F is a UEE has both conjugated and non-conjugated estrogens. Turner et al. then teaches a two path separation method. **Path A** (steps W-Y) requires a hydrophobic solvent that is a "non-solvent" for conjugated estrogens such as benzene (Turner, col 4, lines 50-50) extracting the non-conjugated estrogens. The extraction with benzene can be repeated. The end result is an aqueous phase that is a natural mixture of CEEs that are depleted in NCLC such as non-conjugated flavonoids, non-conjugated isoflavanoids, and non-conjugated norisoprenoids.

estrogens and leaving the conjugated estrogens in the aqueous solution of Step F that are subsequently recovered in steps G-T. **Path B** (steps G-T) extracts the conjugated estrogens from the aqueous solution of the step F UEE using a solvent suitable for conjugated estrogens that has limited solubility in water (Turner, col 4, lines 55-60) such as a butanol (Turner Example 1, Lines 28-34). In Example 1 of Turner et al. Path A is performed on the aqueous solution of Step F first, leaving behind the conjugate estrogens in the aqueous solution of step F. So in summary the key teaching of Turner et al. is that benzene can selectively extract non-conjugated estrogens from an aqueous solution of PMU.

While Turner discloses solvents such as benzene in their method they do not specifically disclose the non-polar solvent ethyl acetate. However it would be obvious to replace benzene with ethyl acetate in view of the teachings by Wang et al., who discloses a method for a liquid-liquid extraction that use ethyl acetate to extract PMU (Wang et al. page 2, lines 15-30).

However in the document by Wang et al., they teach the addition of salt to the aqueous phase to lower the solubility of the conjugated estrogens in the water layer and partition them into the non-aqueous phase (page 2, line 24-26). One of ordinary skill in the art would recognize that without the addition of salt as in the method of Turner, the conjugated estrogens would remain in the aqueous layer since they are more soluble in this phase which is taught by Klaassen et al. (page 254 col 1, paragraph 1 and 2). One of ordinary skill would also recognize that ethyl acetate is an effective non-polar solvent for the separation of phenolics and flavonoids and other hydrophobic compounds from

water soluble compounds such as conjugated estrogen as taught by Hurst et al. (page 228, line 3). So it would have been obvious to modify the method of Turner et al. by using the non-polar solvent ethyl acetate as his hydrophobic "non-solvent" for the liquid-liquid extraction of conjugated estrogens from PMU. The motivation is provided by Turner and the reasonable expectation of success by Wang et al. with support from Klaassen et al.

The Applicant argues that Wang et al. teaches away from replacing ethyl acetate with benzene in the method of Turner et al. The basis of their argument is that Wang et al. teach that the addition of salt forces the conjugated estrogens into the organic phase and not in the aqueous phase. Patents are relevant as prior art for all they contain.

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). Nonpreferred embodiments constitute prior art. Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi*, 440 F.2d 442, 169 USPQ 423 (CCPA 1971). "A known or obvious composition does not become patentable simply because it has been described as an invention in the prior art." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including

somewhat inferior to some other product for the same use." *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994). See M.P.E.P. §2123.

It is acknowledged that the prior art as a whole must suggest the desirability of the invention, but a finding that the prior art as a whole suggests the desirability of a particular method need not be supported by a finding that the prior art suggest that the method claimed is the preferred, or most desirable method. The prior art's mere disclosure of more than one alternative does not constitute a teaching away from the claimed invention because such disclosure does not criticize, discredit, or other wise discourage the solution claimed in the patent application. See *In re Fulton*, 391 F.3d 1195, 73 USPQ2d 1411 (2004).

The art is replete with variations of liquid-liquid extractions and options. Furthermore, Wang et al. is very clear to the reason why they added the salt in their extraction process by stating "the addition of salt to lower the solubility of conjugated estrogens in an aqueous phase, and the liquid-liquid extraction to partition the majority of the conjugated estrogens in the organic phase" (Wang et al. page 2, line 23 to page 3, line 5). Wang et al. teaches that the addition of salt increases the ionic strength of the aqueous phase (page 3 lines 1-3). One of ordinary skill in the art would recognize that increasing the ionic strength results in an increase in the ion pairing of the sulfate moiety on the conjugated estrogens with an available cation. This neutralizes the change of the conjugated estrogen making it more lipophilic, providing it increased solubility in an organic phase as referred to by Wang et al. (page 3, lines 4-8). In summary one of ordinary skill in the art after reading the PMU extraction of Wang et al. extraction process by adding salt to the aqueous phase to lower the solubility of conjugated estrogens in an aqueous phase, and the liquid-liquid extraction to partition the majority of the conjugated estrogens in the organic phase (Wang et al. page 2, line 23 to page 3, line 5).

would understand Wang et al. rational for adding salt in their method and the results of not having salt in their method step. Using this information one of ordinary skill in the art would recognize that the absence of salt in the method of Wang et al. would leave the conjugated estrogens (that have negatively charged sulfate moieties) in the aqueous phase while the non-conjugated estrogens would partition into the organic phase of ethyl acetate.

The Applicant argues that the replacement of benzene with ethyl acetate in the method of Turner et al. is improper. The Applicant asserts that one of ordinary skill in the art would use replace ethyl acetate with butanol in Path B would be more appropriate since "these two solvents [ethyl acetate and butanol] are more comparable than ethyl acetate and benzene" (Applicant's Response, page 8, last paragraph) and provides a table show the physical properties of each of the three solvents as Appendix A.

However this Argument is not persuasive since the primary physical property defining solubility and partitioning behavior of a solute in a solvent is the dielectric constant (as supported by the webpage "Dielectric Constant and Solubility"). The dielectric constants of these solvents are as follows (Wikipedia "Solvent", Properties table of common solvents).

Solvent	Dielectric Constant
Benzene	2.3
Ethyl Acetate	6.0
n-butanol	18

Applicant's Response, page 8, last paragraph. The Applicant provides a table showing physical properties of the three solvents as Appendix A.

However, and as stated above, the primary physical property defining solubility and partitioning behavior of a solute in a solvent is the dielectric

So it is clear by these numbers that benzene and ethyl acetate have much closer dielectric constants than n-butanol and ethyl acetate. Furthermore in the same chart that these values were taken lists both benzene and ethyl acetate as "Non-Polar Solvents" while they list n-butanol as a "Polar Protic Solvent". These teachings contradict the Applicant's assertion that butanol and ethyl acetate "are more comparable".

The remaining claims 11-18 limit the conditions such as pH and solvent ratios for which the method is carried out under. Both Wang et al. and Turner et al. teach a variety of these conditions (Turner see Example 1 and 2, Wang, pg 4, lins 9-26). While the references listed above do not specifically teach the limitations of pH and solvent ratios as seen in claims 11-18, one of ordinary skill in the art would recognize these limitations are result effective variables. Absent any teaching of criticality by the applicant concerning these limitations, it would be *prima facie* obvious that one of ordinary skill in the art would recognize these limitations are result effective variables which can be met as a matter of routine optimization (M.P.E.P. § 2144.05 II).

The method of Turner et al. inherently teach the depletion of the phenolic contents is PMU by the vacuum evaporation of the solvent in Steps A-D. A person of ordinary skill in the art would recognize that phenol, cresols and HPMF are volatile compounds that will evaporate with water during step D of the procedure of Turner et al. This implicitly meets the limitation of claim 1 step a(i). See (MSDS "phenol" Physical and Chemical Properties and ICSC "m-cresol" and "p-cresol" Routes of Exposure as well as Neeb, HPMF Volatility in a vacuum, page 6781, Figure 5). However, Turner et

al. does not teach the depletion of the phenolic contents by solid-phase extraction (SPE). More specifically they do not teach that the SPE is carried out with a non-ionic semipolar adsorption resin or hydrophobized silica gel. Regardless this would be obvious to one of ordinary skill in the art by the time the invention was made in view of the teachings of Ban et al.

Ban et al. successfully depletes the phenolic constituents of cresol and HPMF using SPE (Ban, Abstract and Col 7, see Table). The SPE is performed using RP silica gels with n-octadecyldimethylsiloxyl substituents. While Ban et al. makes no mention of isolating phenol in their SPE process one of ordinary skill in the art would recognize that these type of n-octadecyldimethylsiloxyl silica gels are commonly known as C18 gels and will inherently isolate phenol as well as supported by Fritz et al. who shows that phenol and p-cresol can indeed be isolated by C18 gels (Fritz, Table VI).

SPE with C18 gels and column are well known in the art to treat urines samples as taught by Ben et al. (See Abstract) and Fritz et al. (col 1, lines 15-20). Since Turner et al. already teach a base technique in their patent issued in 1950, before SPE was widely used in the art, it would have been obvious to someone skilled in the art to apply the teachings of Ban et al. and Fritz et al. and use an SPE extraction to prepare the PMU samples for estrogen extraction. Since both techniques are known in the art and SPE is a known method to improve the extraction of conjugated estrogens free of phenolic impurities it would be obvious for one of ordinary skill in the art to apply the teachings of Ban et al. and Fritz et al. to improve the base method of Turner et al. (KSR International Co. v. Teleflex Inc., 550 U.S. --, 82 USPQ2d 1385 (2007)).

SPE with C18 gels and column are well known in the art to treat urines samples as taught by Ben et al. (See Abstract) and Fritz et al. (col 1, lines 15-20). Since Turner et al. already teach a base technique in their patent issued in 1950, before SPE was widely used in the art, it would have been obvious to someone skilled in the art to apply the teachings of Ban et al. and Fritz et al. and use an SPE extraction to prepare the PMU samples for estrogen extraction. Since both techniques are known in the art and SPE is a known method to improve the extraction of conjugated estrogens free of phenolic impurities it would be obvious for one of ordinary skill in the art to apply the teachings of Ban et al. and Fritz et al. to improve the base method of Turner et al. (KSR International Co. v. Teleflex Inc., 550 U.S. --, 82 USPQ2d 1385 (2007)).

Therefore the references listed above renders obvious claims 1, 2, 5, 6, 8-15-19.

In summary no claims, as written, are allowed for this application.

In response to this office action the applicant should specifically point out the support for any amendments made to the disclosure, including the claims (MPEP 714.02 and 2163.06). Due to the procedure outlined in MPEP § 2163.06 for interpreting claims, it is noted that other art may be applicable under 35 U.S.C. § 102 or 35 U.S.C. § 103(a) once the aforementioned issue(s) is/are addressed.

Applicant is requested to provide a list of all copending U.S. applications that set forth similar subject matter to the present claims. A copy of such copending claims is requested in response to this Office action.

CONTACT INFORMATION

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thane Underdahl whose telephone number is (571) 272-9042. The examiner can normally be reached Monday through Thursday, 8:00 to 17:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

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published applications may be obtained from either Private PAIR or Public PAIR.

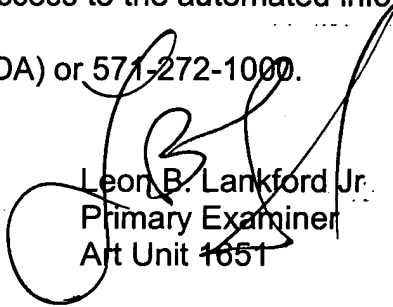
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Thane Underdahl
Art Unit 1651


Leon B. Lankford Jr.
Primary Examiner
Art Unit 1651